

### **REMARKS**

Reconsideration and withdrawal of the rejections of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1 and 50-53 are amended, and claims 56-57 are added; as a result, claims 1-31 and 44-57 are pending in this application.

Support for the amendments to claims 1 and 50-53, is found, for instance, at page 13, lines 19-25, page 19, lines 24-28, and page 20, lines 3-5 and 20-22 of the specification. Support for new claims 56 and 57 is found, for instance, in the example in the specification.

#### **The 35 U.S.C. § 112, First Paragraph, Rejections**

The Examiner rejected claims 1, 8-9, 15-19, 23, 25, and 44-55 under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. Specifically, the Examiner alleges that the specification teaches the structure of only a single representative species of SEQ ID Nos:2, 3 and 4, and fails to describe any other representative species by any identifying characteristics or properties other than the functionality of hybridizing to SEQ ID NO:2, 3 or 4 and to fails describe polypeptides [*sic*] having at least 80%, 85%, 90%, 95% or 97% sequence identity to SEQ ID NO:2, 3 or 4. The Examiner also asserts that there is no support for the primers or probe consisting of 15 to 40 nucleotides which include SEQ ID NO:2, 3 or 4. The Examiner also rejected claims 1, 8-9, 15-19, 23, 25, and 44-55 under 35 U.S.C. § 112, first paragraph, as containing new matter. In particular, the Examiner alleges that there is no support for probes or primers having about 15 to 40 nucleotides with at least 80% identity to SEQ ID NO:2, 3, or 4 or the complement thereof that hybridizes to SEQ ID NO:2, 3, or 4. These rejections are respectfully traversed.

The Examiner is respectfully reminded that Applicant need not teach what is well know to the art. *vanA* sequences, including *vanA*-specific probes and primers, were well known to the art, as were amplification and hybridization assays to detect those and other sequences (see Petrich et al., Mol. Cell Probes, 13:275 (1999) and U.S. Patent No. 6,274,316; both of record, as well as the Table of Contents for Diagnostic Molecular Microbiology: Principles and Applications, Pershing, ed., American Society of Microbiology, 1993 (a copy is enclosed herewith).

Moreover, Applicant's specification clearly identifies the nucleotide sequence corresponding to nucleotides 870 to 896, 851 to 868 and 898 to 917 of *vanA* (see Figure 1 and SEQ ID NOs. 2-4).

The Examiner cannot reasonably contend that the recitation of a primer or probe that forms a hybrid with, and has at least 80% nucleic acid sequence identity to, a particular nucleic acid structure does not convey a common structure or function. Hybrid formation and percent nucleic acid sequence identity between two nucleic acid molecules *clearly* convey a common structure (see, for example, the Table of Contents for Diagnostic Molecular Microbiology: Principles and Applications, Pershing, ed., American Society of Microbiology, 1993; The Polymerase Chain Reaction, Mullis et al., eds., Birkhauser, 1994 (copy enclosed), and Molecular Cloning: A Laboratory Manual, Sambrook et al., eds., Cold Spring Harbor Press, 2001 (copy enclosed)).

The Examiner also cannot reasonably contend that the skilled artisan cannot envision the detailed structure of nucleic acid sequences with at least 80% nucleic acid sequence identity to SEQ ID NO:2, 3 or 4. For instance, SEQ ID NO:2 has 18 nucleotides, SEQ ID NO:3 has 27 nucleotides, and SEQ ID NO:4 has 20 nucleotides. A sequence with 3 nucleotide substitutions relative to SEQ ID NO:2 has 83% identity thereto, a sequence with 6 nucleotide substitutions relative to SEQ ID NO:3 has 81% identity thereto, and a sequence with 4 nucleotide substitutions relative to SEQ ID NO:4 has 80% identity thereto.

Moreover specifically, SEQ ID NO:2 corresponds to CCGGTGGCAGCTACGTTT (18 nucleotides). 80% of 18 is 14.4. Therefore, probes within the scope of invention include those with up to 3 nucleotide substitutions in SEQ ID NO:2. The following represents a set of variants of SEQ ID NO:2 with a single substitution (indicated by underlining):

C~~C~~GGTGGCAGCTACGTTT, C~~A~~GGTGGCAGCTACGTTT, and

C~~T~~GGTGGCAGCTACGTTT. The following represents a set of variants of SEQ ID NO:2 with

two substitutions (indicated by underlining): C~~C~~GGTGGCAGCTA~~G~~GTTT, C~~A~~GGTGGCAG

CTA~~A~~GTTT, and C~~T~~GGTGGCAGCTA~~T~~GTTT, and the following represents a set of variants

of SEQ ID NO:2 with three substitutions (indicated by underlining): C~~C~~GGGGGCAG

CTA~~G~~GTTT, C~~A~~GG~~A~~GGCAGCTA~~A~~GTTT, and C~~T~~GG~~C~~GGCAGCTA~~T~~GTTT.

Given that the Example in the specification discloses the use of SEQ ID Nos. 2-4 in a method to detect *vanA* sequences in a sample, and that the specification discloses that sequences

with close structural relatedness to SEQ ID Nos. 2-4, i.e., those with at least 80% nucleic acid sequence identity to the 18 nucleotides corresponding to SEQ ID NO:2, the 27 nucleotides corresponding to SEQ ID NO:3, and the 20 nucleotides corresponding to SEQ ID NO:4, are useful in the claimed methods, one of skill in the art would recognize that Applicant was in possession of the claimed invention.

It is unclear to Applicant why claims 54-55 do not satisfy the written description requirement, as they are directed to primers and probes with a specific sequence.

The fundamental inquiry with regard to new matter is whether the material added by amendment was inherently contained in the original application. *Litton Sys., Inc. v. Whirlpool Corp.*, 728 F.2d 1423, 1438, 221 U.S.P.Q. 97, 106 (Fed. Cir. 1984). The issue is not whether a specific new word of a claim was used in the specification as filed but whether the concept expressed by the word was present. *In re Anderson*, 471 F.2d 1237, 176 U.S.P.Q. 331 (C.C.P.A. 1973).

As filed, claim 1 recited that the *vanA*-specific oligonucleotide probe comprises sequences which include sequences substantially corresponding to nucleotides 870 to 896 of the *vanA* gene, the complement thereof, or a portion thereof, sequences substantially corresponding to nucleotides 851 to 868 of the *vanA* gene, the complement thereof, or a portion thereof, or sequences substantially corresponding to nucleotides 898 to 917 of the *vanA* gene, the complement thereof, or a portion thereof.

Claim 32 (as filed) is directed to an oligonucleotide composition comprising a first oligonucleotide comprising sequences substantially corresponding to nucleotides 870 to 896 of the *vanA* gene, the complement thereof, or a portion thereof, an oligonucleotide comprising sequences substantially corresponding to nucleotides 851 to 868 of the *vanA* gene the complement thereof, or a portion thereof, an oligonucleotide comprising sequences substantially corresponding to nucleotides 898 to 917 of the *vanA* gene, the complement thereof, or a portion thereof, or a combination thereof, wherein the oligonucleotide hybridizes under stringent hybridization conditions to *vanA* DNA. Claim 34 (as filed) depends on claim 32, and is directed to at least one oligonucleotide that has the length and sequence of any of SEQ ID NOs:2-4.

Pages 10 and 11 of the specification disclose that:

An "oligonucleotide" is a polynucleotide having two or more nucleotide subunits covalently joined together.

A "primer" is a single-stranded polyoligonucleotide that combines with a complementary single-stranded target to form a double-stranded hybrid, which primer in the presence of a polymerase and appropriate reagents and conditions, results in nucleic acid synthesis.

A "probe" is a single-stranded polynucleotide that combines with a complementary single-stranded target polynucleotide to form a double-stranded hybrid.

Page 6 of the specification discloses:

In one embodiment, the oligonucleotides of the invention include sequences substantially corresponding to nucleotides 851 to 868 of the *vanA* gene (SEQ ID NO:2; an exemplary *vanA* gene has SEQ ID NO:1 from *E. faecium* pIP816 gi 43335, also see Figure 1, Accession No. X56895 which corresponds to SEQ ID NO:11), or the complement thereof, or a portion thereof; sequences substantially corresponding to nucleotides 870 to 896 of the *vanA* gene (SEQ ID NO:3), the complement thereof, or a portion thereof; sequences substantially corresponding to nucleotides 898 to 917 of the *vanA* gene (SEQ ID NO:4), the complement thereof, or a portion thereof (emphasis added).

The Example discloses the use of primers having SEQ ID Nos. 2 and 4 to amplify *vanA*-specific sequences in a sample and a probe having SEQ ID NO:3 to detect *vanA*-specific sequences in a sample.

In the Amendment filed on May 30, 2007, Applicant indicated that support for the amendments to claim 1 is found, for instance, at page 13, lines 19-25, page 19, line 24-page 20, line 2, and page 20, lines 3-5 and 20-22 of the specification. Page 13 discloses that:

One skilled in the art will understand that probes or primers that substantially correspond to a reference sequence or region can vary from that reference sequence or region and still hybridize to the same target nucleic acid sequence. Probes of the present invention substantially correspond to a nucleic acid sequence or region if the percentage of identical bases or the percentage of perfectly complementary bases between the probe and its target sequence is from 100% to 80% or from 0 base mismatches in a 10 nucleotide target sequence to 2 bases mismatched in a 10 nucleotide target sequence. In one embodiment, the percentage is from 100% to 85%. In another embodiment this percentage is from 90% to 100%; and in yet other embodiments, this percentage is from 95% to 100% (emphasis added).

Page 19 discloses that:

Preferred methods for detecting the presence of the *vanA* or *vanB* gene, include the step of contacting a test sample with at least two oligonucleotide primers under conditions that

preferentially amplify *vanA* and/or *vanB* sequences....While oligonucleotides probes of different lengths and base composition may be used for detecting the *vanA* gene or the *vanB* gene, preferred oligonucleotides have lengths from 15 up to 40 nucleotides and are sufficiently homologous to the target nucleic acid to permit amplification of a *vanA* or *vanB* template and/or hybridization to such a template under high stringency conditions (emphasis added).

Page 19 also discloses that:

[T]he specific sequences described herein also may be provided in a nucleic acid cloning vector or transcript or other longer nucleic acid and still can be used for amplifying or detecting the *vanA* gene or the *vanB* gene, i.e., the probes may include sequences unrelated to the *vanA* or *vanB* gene, for instance at the 5' end, the 3' end, or both the 5' and 3' ends. Likewise, primers may include sequences unrelated to the *vanA* gene and/or the *vanB* gene, e.g., at the 5' end (emphasis added).

Page 20 discloses that:

Preferred primers and probes have sequences of up to 40 nucleotides in length and preferably have at least 17 contiguous nucleotides corresponding to sequences in the *vanA* gene or the *vanB* gene, or the complement thereof... Preferably, the probes specifically hybridize to *vanA* or *vanB* DNA only under conditions of high stringency. Under these conditions only highly complementary nucleic acid hybrids will form (i.e., those having at least 14 out of 17 bases in a contiguous series of bases being complementary). Hybrids will not form in the absence of a sufficient degree of complementarity (emphasis added).

Thus, the specification clearly provides support for the recited probes and primers.

Accordingly, withdrawal of the § 112, first paragraph, rejections is respectfully requested.

*The 35 U.S.C. § 112, Second Paragraph, Rejections*

The Examiner rejected claims 1, 8-9, 15-19, 23, 25, and 44-55 under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner asserts that 1) claims 1 and 50-53 are unclear, as claims 1 and 50-53 recite the broad limitation of having 15 to 40 nucleotides, yet SEQ ID NOs:2, 3 and 4 do not have 40 nucleotides (the sequences have 18, 27 and 20 nucleotides, respectively), and the claims and specification fail to disclose what the other nucleotides are; 2) the term "hybridizes" in the claims is a relative term which renders the claims

indefinite; and 3) the phrase "one which under the same conditions hybridizes" in claim 1 is a relative phrase which renders the claims indefinite. These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

The claims no longer recite "one which under the same conditions hybridizes", thereby obviating the § 112(2) rejection thereof.

It is Applicant's position that the metes and bounds of the recited primers and probe are clear. That is, the probe is a *vanA*-specific oligonucleotide that forms a hybrid with *vanA* nucleic acid in a sample. The probe consists of 15 to 40 nucleotides and has a sequence with at least 80% nucleic acid sequence identity to SEQ ID NO:3 or the complement of SEQ ID NO:3. The probe is one which forms a hybrid with SEQ ID NO:3 or its complement. Thus, the probe is of a particular length and has sequence homology to SEQ ID NO:3 or its complement.

The two primers are oligonucleotides that amplify *vanA* nucleic acid. The primers consist 15 to 40 nucleotides. One (the first) primer has a sequence with at least 80% nucleic acid sequence identity to SEQ ID NO:2, and the other (the second) primer has a sequence with at least 80% nucleic acid sequence identity to SEQ ID NO:4. The first primer forms a hybrid with the complement of SEQ ID NO:2, and the second primer forms a hybrid with the complement of SEQ ID NO:4. Hence, the primers are of a particular length and have sequence homology to SEQ ID NO:2 or SEQ ID NO:4.

For instance, a nucleic acid sequence which consists of 15 contiguous nucleotides of SEQ ID NO:2 (SEQ ID NO:2 has 18 nucleotides) has a sequence with 15 nucleotides having 100% nucleic acid sequence identity to SEQ ID NO:2; a nucleic acid sequence which consists of 15 nucleotides, 14 of which are identical in sequence to those in SEQ ID NO:2 and one of which is different, has a sequence with 15 nucleotides having at least 80% nucleic acid sequence identity to SEQ ID NO:2; and a nucleic acid sequence which consists of 40 nucleotides, 15 of which are identical in sequences to those in SEQ ID NO:2, has a sequence with 15 nucleotides having 100% nucleic acid sequence identity to SEQ ID NO:2.

Moreover, one of skill in the art understands that sequences other than those needed for specificity of a probe or primer may be included with the probe or primer, e.g., a restriction enzyme site may be included in a primer sequence to facilitate cloning of sequences amplified with the primer. For example at page 19 of the specification, it is disclosed that:

the specific sequences described herein also may be provided in a nucleic acid cloning vector or transcript or other longer nucleic acid and still can be used for amplifying or detecting the *vanA* gene or the *vanB* gene, i.e., the probes may include sequences unrelated to the *vanA* or *vanB* gene, for instance at the 5' end, the 3' end, or both the 5' and 3' ends. Likewise, primers may include sequences unrelated to the *vanA* gene and/or the *vanB* gene, e.g., at the 5' end.

Therefore, the metes and bounds of the recited probe and primers is clear.

It is Applicant's position that one of skill in the art would understand the metes and bounds of the term "hybridizes" as it is conventionally used in the art. See, e.g., Petrich et al. *supra*, and U.S. Patent No. 6,274,316, *supra*, which disclose primers or probes that hybridize to *vanA* sequences in a biological sample. It is also Applicant's position that the selection of amplification and/or hybridization conditions specific for *vanA* sequences is conventional in the art. See, for instance, Petrich et al., *supra*, Patel et al., "Multiplex PCR Detection of *vanA*, *vanB*, *vanC*-1, and *vanC*-2/3 Genes in Enterococci", *J. Clin. Microbiology*, 35: 703 (1997); Petrich et al., "Effect of Routine Use of a Multiplex PCR for Detection of *vanA*- and *vanB*- Mediated Enterococcal Resistance on Accuracy, Costs and Earlier Reporting", *Diagnostic Microbiology and Infectious Disease*, 41:215 (2001); and Satake et al., "Detection of Vancomycin-Resistant Enterococci in Fecal Samples by PCR", *J. Clin. Microbiology*, 35:2325 (1997); all of record.

Moreover, one of skill in the art is aware that more than one set of conditions can result in the specific hybridization of two nucleic acid sequences.

Even if, assuming for the sake of argument, the metes and bounds of the term "hybridizes" was not readily recognizable to one skilled in the art, the specification discloses particular conditions at page 20 (for amplification reactions with primers) and pages 24-25 (for probes). Thus, the scope of the claims would be clear to a person of skill in the art, particularly when read in light of the specification.

Nevertheless, to advance the application, "hybridizes" has been deleted from claim 1.

Accordingly, withdrawal of the § 112, second paragraph, rejections is respectfully requested.

**CONCLUSION**

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

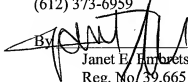
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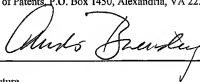
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# Diagnostic Molecular Microbiology

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## PRINCIPLES AND APPLICATIONS

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AMERICAN SOCIETY FOR MICROBIOLOGY  
WASHINGTON, D.C.

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Rochester, MN 55905

**Library of Congress Cataloging-in-Publication Data**

Diagnostic molecular microbiology : principles and applications / edited by  
David H. Persing . . . [et al.].

p. cm.

Includes index.

ISBN 1-55581-056-X

1. DNA probes--Diagnostic use. 2. Diagnostic microbiology--Technique. 3. Nucleic acid hybridization. 4. Communicable diseases--Diagnosis--Laboratory manuals. I. Persing, David H. QR69.D4D5 1993  
616.9'047583--dc20

92-38523

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Cover illustration by Tomo Narashima

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# The Polymerase Chain Reaction

Kary B. Mullis  
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Editors

Foreword by James D. Watson

With 112 Illustrations

Birkhäuser  
Boston • Basel • Berlin


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Printed on acid-free paper.

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ISBN 0-8176-3607-2 (hardcover)  
ISBN 3-7643-3607-2 (hardcover)

ISBN 0-8176-3750-8 (softcover)  
ISBN 3-7643-3750-8 (softcover)

Typeset by Sherman Typography, York, PA.  
Printed and bound by The Maple Press Company, York, PA.  
Printed in the United States of America.

9 8 7 6 5 4 3 2 1

*Cover illustration:* Based on a photograph taken by Kary Mullis in a museum in Cologne. "The mosaic had been taken from Italy by the Germans. I think it was from Pompeii. I saw a similar design still intact in its original location in Herculaneum but had no camera that day. Vesuvius covered both cities in 79 A.D. I would guess that the structure of DNA was probably worked out about two thousand years before Watson was born and therefore nineteen hundred and eighty-eight years before Crick. The Romans, however, seemed to think that atoms were square, and most likely the significance of the structure did escape their notice. Of course, this was long before Avery."



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David W. Russell

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COLD SPRING HARBOR LABORATORY PRESS  
Cold Spring Harbor, New York

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Cold Spring Harbor, New York

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COLD SPRING HARBOR LABORATORY PRESS  
Cold Spring Harbor, New York

# Molecular Cloning

A LABORATORY MANUAL

THIRD EDITION

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Printed in the United States of America

**Front cover (paperback):** The gene encoding green fluorescent protein was cloned from *Aequorea victoria*, a jellyfish found in abundance in Puget Sound, Washington State. This picture of a 50-mm medusa was taken on color film by flash photography and shows light reflected from various morphological features of the animal. The small bright roundish blobs in the photograph are symbiotic amphipods living on or in the medusa. The bright ragged area in the center is the jellyfish's mouth.

Bioluminescence from *Aequorea* is emitted only from the margins of the medusae and cannot be seen in this image. Bioluminescence of *Aequorea*, as in most species of jellyfish, does not look like a soft overall glow, but occurs only at the rim of the bell and, given the right viewing conditions, would appear as a string of nearly microscopic fusiform green lights. The primary luminescence produced by *Aequorea* is actually bluish in color and is emitted by the protein aequorin. In a living jellyfish, light is emitted via the coupled green fluorescent protein, which causes the luminescence to appear green to the observer.

The figure and legend were kindly provided by Claudia Mills of the University of Washington, Friday Harbor. For further information, please see Mills, C.E. 1999-2000. Bioluminescence of *Aequorea*, a hydromedusa. Electronic Internet document available at <http://faculty.washington.edu/cemills/Aequorea.html>. Published by the author, web page established June 1999, last updated 23 August 2000.

**Back cover (paperback):** A portion of a human cDNA array hybridized with a red fluor-tagged experimental sample and a green fluor-tagged reference sample. Please see Appendix 10 for details. (Image provided by Vivek Mittal and Michael Wigler, Cold Spring Harbor Laboratory.)

## Library of Congress Cataloging-in-Publication Data

Sambrook, Joseph.

Molecular cloning : a laboratory manual / Joseph Sambrook, David W.

Russell. -- 3rd ed.

p. : cm.

Includes bibliographical references and index.

ISBN 0-87969-576-5 (cloth) -- ISBN 0-87969-577-3 (pbk)

1. Molecular cloning--Laboratory manuals.

[DNLN: 1. Cloning, Molecular--Laboratory Manuals. QH 440.5 S187m

2001] I. Russell, David W. (David William), 1954- . II. Title.

QH442.2 .S26 2001

572.8--dc21

00-064380

10 9 8 7 6 5 4 3 2 1

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